IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Before the United States International
Preliminary Examining Authority
for the Patent Cooperation Treaty

Applicant: **Drexel University**
International
Application No.: **PCT/US99/28403**

International
Filing Date: **30 November 1999**

Attorney Ref.: **DRE-0019**

Honorable Commissioner of
Patents and Trademarks
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"Express Mail" Label No. EL777535010US
Date of Deposit - 06 November 2000

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Response to Written Opinion

This is in response to the Written Opinion mailed 08 September 2000. Reconsideration of this application is respectfully requested.

Claims 1-4 have been acknowledged to have both novelty and industrial application.

However, claims 1-4 have been suggested to lack inventive step under PCT Article 33(3) as being obvious over Hoffmann-LaRoche AG (N-Genes seq.: ID No. Q10956) and Synergen Inc. (N-Geneseq; ID No Q10907) in view of Duff et al. The Examiner suggests that Hoffmann-LaRoche AG discloses the claimed sequence of the tumor necrosis factor (TNF) alpha 2 receptor and Synergen, Inc. teaches the claimed polymorphism in the

tumor necrosis factor sequence. Further the Examiner states that Duff et al. teach tumor necrosis factor involvement in bone remodeling, and that it would have been obvious to one skilled in the art to apply the teaching of Duff et al. to the sequences taught by Hoffmann-LaRoche AG and Synergen, Inc. to detect specific sequences involved with osteoporosis. Applicant disagrees.

Applicant's invention is a method for identifying individuals at risk of developing osteoporosis comprising assessing the genotype of tumor necrosis factor alpha 2 receptor gene in a sample of DNA from an individual. Applicant further claims a method of identifying individuals at risk of developing osteoporosis comprising assessing the genotype of tumor necrosis factor alpha 2 receptor gene wherein the genotype comprises a polymorphism at nucleotides 593, 598, and 620 in exon 10 of the gene.

Hoffman-LaRoche AG teaches a sequence encoding a 40kD TNF inhibitor with polymorphisms at nucleotides 598 and 620. The sequence is taught as useful in pharmaceutical products for antibody production. It is not taught as useful in identification of individuals at risk for osteoporosis.

Synergen, Inc. teaches a sequence encoding a 40kD TNF inhibitor with polymorphisms at nucleotides 593 and 598. The sequence is taught as able to be inserted into expression vectors for preparations of TNF inhibitor. Synergen, Inc. does not teach a polymorphism at nucleotide 620. There is no teaching that the sequence is useful in identifying those at risk for osteoporosis.

Duff et al. teaches a method for predicting low bone mineral density. The method includes the steps of isolating DNA from a subject and determining the DNA polymorphism pattern of the gene IL-1RNN that codes for IL-1 receptor antagonist IL-1ra. Duff et al. further discloses a kit for

the identification of a susceptibility to osteoporosis based upon identification of a polymorphism pattern at IL-1RN. Duff et al. does not teach a method of identifying individuals at risk of developing osteoporosis comprising assessing the genotype of tumor necrosis factor alpha 2 receptor gene. While there is generalized statement that IL-1 and tumor necrosis factor are involved in the regulation of bone remodeling, there is no suggestion that the tumor necrosis factor alpha 2 receptor gene would be at all useful in identifying individuals at risk of developing osteoporosis.

None of the recited art teaches tumor necrosis factor alpha 2 receptor gene as being indicative of osteoporosis. Accordingly, these references when combined fail to provide the requisite teaching to anticipate or render obvious a claim drawn to a method for identifying individuals at risk of developing osteoporosis comprising assessing the genotype of tumor necrosis factor alpha 2 receptor gene in a sample of DNA.

Further the sequence taught by Hoffman-LaRoche AG has polymorphisms at nucleotides 598 and 620. The Synergen, Inc. sequence encodes polymorphisms at nucleotides 593 and 598. There is no teaching, suggestion or motivation found in the recited references to combine the sequences of Hoffman-LaRoche AG and Synergen, Inc. to arrive at Applicant's teachings in claims 2 and 4, i.e., a sequence with polymorphisms at nucleotides 593, 598 and 620. There could be no reasonable manner of predicting an indicator of osteoporosis with three specific polymorphism sites based upon the recited art. Accordingly, it would not have been obvious for one skilled in the art to apply the teaching of Duff et al. to a hybrid of the sequences taught by Hoffman-LaRoche AG and Synergen, Inc. to arrive at a method and kit for the detection of specific sequences involved with osteoporosis.

Thus claims 1-4 should be deemed to meet the requirements of PCT Article 33(3).

Respectfully submitted,

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Date: 06 November 2000

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